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Case Report

Life threatening intracerebral hemorrhage with isometheptene mucate, dichlorophenazine and acetaminophen combination therapy

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ABSTRACT

A 45 year old female with no stroke risk factors suffered a massive intracerebral hemorrhage (ICH) after ingesting Midrin – a combination of isometheptene mucate, dichlorophenazine and acetaminophen. Neuroimaging revealed no evidence of structural disease or underlying vasculopathy. This is the first reported case of isometheptene induced ICH in the absence of underlying cerebrovascular disease. Physicians must be aware of the potential for this complication, and inquire about the use of isometheptene in unexplained cerebral hemorrhages. Neurological communities in countries with nonprescription isometheptene should discourage unsupervised or excessive use of the drug.

1. Introduction

Isometheptene, singly or combined with other drugs, is a common headache medication available by prescription or over the counter in North and South America, Europe and Asia (Table 1). In the United States, Midrin – the combination acetaminophen 325 mg, dichlorophenazine 100 mg and isometheptene mucate 65 mg – is frequently prescribed for the treatment of migraine and tension headaches.[1] Acetaminophen exerts an analgesic effect against headaches by raising the threshold to painful stimuli. Dichlorophenazine has a mild sedative effect owing to the hydrolysis product chloral hydrate which produces relaxation and blunts emotional stimuli influencing the perception of pain. Isometheptene is an unsaturated aliphatic sympathomimetic amine that acts by constricting dilated cranial and cerebral arterioles, thereby reducing the stimulus that precipitates vascular headaches. It is the presence of isometheptene – not the specific components of any particular combination – that is concerning due to the strong association between sympathomimetics and stroke.

Isometheptene may be associated with reversible cerebral arterial vasospasm and postpartum cerebral vasculopathy (PCV).[2–4] This is the first reported case of isometheptene induced intracerebral hemorrhage (ICH) in the absence of underlying cerebrovascular disease.

2. Case report

A 45 year old white female presented to her family physician for evaluation of modest weight gain, and noted a longstanding history of occasional headaches. Past medical history was unremarkable including no medications, no allergies and no tobacco or illicit drug use. Examination was normal. Hematologic studies demonstrated hypothyroidism. Synthroid and Midrin were prescribed. Several weeks later she attempted suicide by slashing her left wrist and ingesting 15 Midrin tablets within several hours. EMS documented BP 112/64, P 132, and estimated a 1 L blood loss. Emergency staff described a flaccid left arm. Brain CT demonstrated a deep right fronto-parietal ICH greater than 3 cm diameter with intraventricular extension and leftward shift (Fig. 1). Angiography revealed a corresponding avascular mass effect with no evidence of any other abnormality. Urine toxicology screening reacted to the amphetamine class, but follow-up gas chromatography was negative. The initial false positive was attributed to isometheptene's sympathomimetic properties. Treatment included ventriculostomy, craniotomy and stereotactic hematoma evacuation. The cognitive impairment and hemiparesis did not significantly improve over the ensuing 2 years.

3. Discussion

The literature is replete with cases of sympathomimetic drug use and abuse causing or associated with cerebral ischemia and hemorrhage. Amphetamines are a well established cause of

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Table 1
Isometheptene containing drugs in several countries.[a]

United States	Midrin[b]	Isometheptene, dichlorophenazine, acetaminophen
United States	MigraTen	Isometheptene, caffeine, acetaminophen
England	Midrid	Isometheptene, paracetamol
Ireland	Midrid	Isometheptene, paracetamol
Italy	Octinum	Isometheptene
Brazil	Neosaldina	Isometheptene, dipyrone, caffeine
Hong Kong	Migraphen	Isometheptene, dichlorophenazone, paracetamol

[a] A host of internet pharmacy sites ensure worldwide access to several proprietary combinations containing isometheptene mucate.
[b] Other generic names include: amidrine, duradrin, epidrin, iso-acetazone, isocom, midchlor, migrapap, migratine, migrazone, migrend, migrex, migquin and mitride.

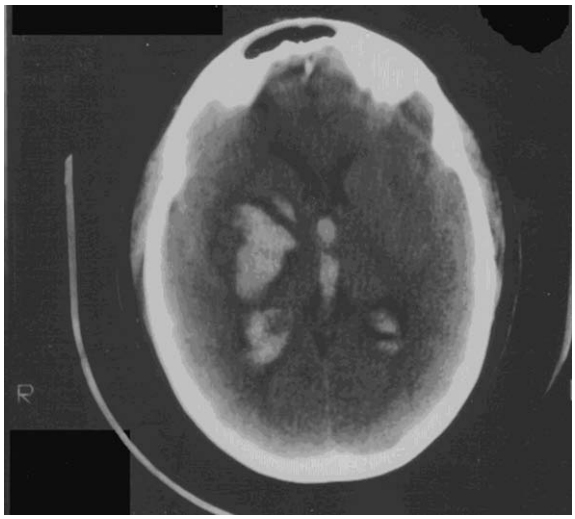

Fig. 1. CT demonstrating ICH.

cerebrovascular disease, especially hemorrhagic stroke.[5] Phenylpropanolamine (PPA) and ephedrine, structural analogues to amphetamines, have been linked to stroke for three decades. The Hemorrhagic Stroke Project multicenter case-control study demonstrated that PPA in appetite suppressants, and possibly in cold remedies, represented an independent risk factor for intracerebral and subarachnoid hemorrhage in women.[6] The Food and Drug Administration (FDA) banned PPA containing products in 2001. A consecutive stroke registry subsequently documented the association between sympathomimetic (primarily PPA containing) cold and cough medications and predominantly hemorrhagic stroke.[7] More recently, a multicenter case-control study concluded that PPA containing cold remedies increased the risk of hemorrhagic stroke.[8] Ephedrine is linked to ischemic and hemorrhagic stroke.[9,10] Uncontrolled evidence suggested that ephedra alkaloid derivatives in dietary supplements may increase the risk for adverse cardiovascular events and strokes.[11] The Hemorrhagic Stroke Project data, although not designed to evaluate ephedra, confirmed an association between higher doses of ephedra and hemorrhagic stroke.[12] Case reports continued linking ephedra to stroke.[13] The FDA imposed a 2004 ban on these products. Manufacturers responded by marketing "ephedra-free" supplements containing the sympathomimetic synephrine, now associated with ischemic stroke.[14] Myriad anecdotal reports link other sympathomimetics to stroke, including pseudoephedrine, phenteramine with and without fenfluramine and some topical intranasal drugs (oxymetazoline and phenoxazolide).[7] However, there is a striking paucity of literature on the relationship between isometheptene and cerebrovascular disease. A multiple database search of isometheptene yields three stroke cases.

In one, a 43 year old man developed angiographically documented reversible cerebral arterial vasospasm with left occipital infarction after taking 23 sumatriptan succinate and 32 Midrin tablets over 7 days.[2] It is impossible to ascertain whether Midrin played any role in the stroke since serotonergic drugs themselves are associated with vasculopathy.[15]

The other two cases suggested an association between isometheptene and PCV. A 32 year old woman presenting 5 days postpartum with headaches and nausea was treated with intravenous chlorpromazine and advised to take Midrin.[4] She ingested eight tablets in 24 h and suffered "neurological deterioration" with generalized tonic–clonic seizures. MRI demonstrated increased bilateral occipital signal on T2 images with no evidence of hemorrhage. Angiography revealed widespread segmental cerebral vasoconstriction. Her headache resolved on acetaminophen. MRI 10 days later was normal. A 38 year old woman developed headaches during her last week of pregnancy and began taking one tablet daily of the nonprescription combination isometheptene mucate 30 mg, dipyrone 300 mg and caffeine 30 mg.[3] After nine weeks, she suffered an intense throbbing headache, vomiting, and blurred vision. MRI demonstrated a hyperintense nodular lesion on gadolinium enhanced T1 images "suggestive of ICH." Angiography revealed focal segmental intracranial vasoconstrictions in multiple vessels. She discontinued isometheptene and 6 months later had "occasional slight frontal headache" with a normal CT and angiogram. Neither case implicates isometheptene as the causative stroke factor since PCV occurs in the absence of sympathomimetics, and is inherently associated with cerebral ischemia and hemorrhage. However, isometheptene may have precipitated or aggravated the PCV thereby leading to the vascular events.

In the instant case, a patient with no stroke risk factors suffered an ICH shortly after ingesting Midrin, and neuroimaging excluded structural lesions or vasculopathy. These facts suggest that Midrin caused the ICH. There are obscure causes of spontaneous ICH which makes it impossible to rule out every other possible etiology with absolute certainty; however, it would be exceedingly unlikely that she suffered one of these extraordinarily rare events at the precise moment of taking Midrin and slashing her wrist.

The patient probably ingested 15 Midrin tablets within a few hours based on the prescription, time course of events and amount remaining in the bottle. She saw her physician 2 days before the suicide attempt and had no complaints of headache, and thus presumably no reason to take any of the prescription. Moreover, it would be illogical to conclude that she took a therapeutic dose as part of a suicide attempt; she likely ingested the amount missing from the bottle. Regardless, the exact amount may be unimportant – numerous reports describe stroke following excessive and therapeutic doses of various sympathomimetic drugs, supporting the idea that even recommended Midrin doses may cause ICH in select patients.

The limited reports of isometheptene and stroke may reflect a rare association; however, if isometheptene tracks the history of other sympathomimetics, Midrin related complications may simply be under-recognized. This warrants careful observation, especially since Midrin will probably be increasingly prescribed after a multicenter, double-blind, randomized, parallel group study concluded it was safe and offered some advantages over sumatriptan in mild to moderate migraine.[16]

4. Conclusion

Physicians must be aware of the potential for isometheptene induced ICH, and inquire about the use of this sympathomimetic in

unexplained hemorrhages. These seemingly innocuous drugs are gaining in popularity and, in fact, being mainstreamed as a primary treatment option for mild to moderate migraine headache. As more patients take the drugs, neurological complications including ICH are likely to be seen more frequently. It may be beneficial to establish a registry of isometheptene related complications and thus avoid some of the confusion that has plagued other sympathomimetic drugs. Additionally, the neurological communities in countries with nonprescription isometheptene should discourage unsupervised or excessive use of the drug.

Conflicts of Interest

None declared.

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None.

Ethical Approval

Not applicable.

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